PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of Fatty Liver Index with risk of Incident Type 2 Diabetes by Metabolic Syndrome Status in an Eastern Finland Male Cohort - a Prospective Study
AUTHORS	Olubamwo, Olubunmi; Virtanen, Jyrki K.; Pihlajamaki, Jussi; Tuomainen, Tomi-Pekka

VERSION 1 – REVIEW

REVIEWER	Didac Mauricio Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
REVIEW RETURNED	20-Oct-2018

GENERAL COMMENTS	The article by Olubamwo et al addresses the question of whether metabolic syndrome status may influence the association of fatty liver with incident type 2 diabetes. To answer the main objective, the authors analysed the prospective Kuopio Ischaemic Heart Disease Risk Factor Study cohort. The methodology used is sound, and the paper is well-written. The final conclusion is that FLI predicts the development of T2D, specifically in men without metabolic syndrome. I have the following questions/issues that need to be addressed by the researchers: - After the application of the exclusion criteria, 162 men with a history of diabetes were excluded. The authors should clarify whether they excluded just subjects with self-reported diabetes (including use of hypoglycaemic agents), or whether they also excluded those subjects with fasting blood glucose concentrations > 125 mg/dl. If the latter was not the case, subjects with glycaemic values indicative of a diagnosis of diabetes at baseline should be excluded. In addition, it would be useful for the reader to know the glycaemic status of all study participants at baseline. - The major factor indicating the risk of progression to diabetes is impaired glycaemia itself. In addition, glycaemia may be indicative of how close to the diagnosis of diabetes is a given subject. Therefore, although fasting glucose was included in most of the models, those without glucose as a confounding variable are not meaningful (e.g. model 1 in tables 2, 3 and 4). Moreover, there is an important issue affecting models shown in table 4; as glucose is already included as one of the criteria of MS, it is redundant to include a factor twice a model. Therefore, the researchers should include another model leaving out glucose from the definition of MS in table 4. - The researchers chose not to exclude men with high alcohol intake. I would recommend excluding these subjects from the main analyses, as these participants may have alcoholic fatty liver disease (not NAFLD). Further, although some lifestyle indicators were included, alcohol intake may be associated with other poor

	health-related behaviours. Alternatively, the authors should explain the reason for including these subjects and perform the analyses included in table 4, also excluding men with high alcohol intake. - Finally, please, check the use of the term "subjects" throughout the manuscript. This term should be substituted by the term "men", especially in the conclusions. This is more informative to the reader - The discussion is too long.

REVIEWER	Dimitrios Koutoukidis University of Oxford, UK
REVIEW RETURNED	15-Feb-2019

GENERAL COMMENTS	This paper shows the association between metabolic syndrome, a liver biomarker (Fatty liver index) and incidence of diabetes. This is a clearly written paper, with a sound analysis, and will be a useful contribution for clinicians and researchers in this field. Major comment I suggest authors run an additional sensitivity analysis excluding smokers given that smoking can be have a large confounding effect in observational studies? This will strengthen the robustness of their findings. Can you also please revise your baseline results which state that there are less smokers in the high FLI group, as this was not statistically significant. Minor comments Abstract line 17: Please add "for T2D" following increased risk.

REVIEWER	Ellen Toth University of Alberta, Canada
REVIEW RETURNED	18-Feb-2019

GENERAL COMMENTS	The limitation of not studying women is very significant: could the authors comment further on the justification for this? As far as the outcome T2DM, was self report sufficient or did there need to be confirmation in registries? How often was T2DM ascertained by the various methods? Neither FLI nor MS are "diseases" or even "conditions"... rather constellations of risk factors. Pending confirmation of statistical methods, and ? understanding the differences between this analysis and that of Karajamaki, would the authors comment from a health systems perspective on which parameters / risk factors would be most cost-effective to screen for in asymptomatic patients (men), and when further studies might be required? OGTT re T2DM? Ultrasound / other radiology / biopsy? re NAFLD/NASH?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
RESPONSE:
We thank the reviewers for their detailed review, insightful comments and suggestions.
To Reviewer 1

The authors should clarify whether they excluded just subjects with self-reported diabetes (including use of hypoglycaemic agents), or whether they also excluded those subjects with fasting blood glucose concentrations > 125 mg/dl. Subjects with glycaemic values indicative of a diagnosis of diabetes at baseline should be excluded. In addition, it would be useful for the reader to know the glycaemic status of all study participants at baseline.

RESPONSE:
Subjects with self-reported physician diagnosed type 2 diabetes were excluded at baseline. The range of values of the fasting blood glucose for the eligible men was between 3.1 mmol/l (minimum) and 6,2 mmol/l (or 112mg/dl) (maximum). The glycaemic values of all eligible subjects are within normal range. Therefore, we had avoided selection bias with respect to baseline Type-2-diabetes-status. We have now stated the range of values of baseline fasting glucose concentration in the first paragraph of the results section of the manuscript, to clarify any doubts.

The major factor indicating the risk of progression to diabetes is impaired glycaemia itself. In addition, glycaemia may be indicative of how close to the diagnosis of diabetes is a given subject. Therefore, although fasting glucose was included in most of the models, those without glucose as a confounding variable are not meaningful (e.g. model 1 in tables 2, 3 and 4).
Therefore, the researchers should include another model leaving out glucose from the definition of MS in table 4.

RESPONSE:
We have removed models without glucose as confounding variable from Table2 and table 3. We have maintained models without glucose as confounding variable in Table 4 because, as the reviewer pointed out, glucose is a component of metabolic syndrome and it would be redundant to include a factor twice a model.
As fasting glucose concentration is a component of metabolic syndrome, excluding glucose from the definition of metabolic syndrome in the analyses presented in table 4 will leave out some subjects, introduce other issues and complicate interpretation. Therefore, we have re-analyzed model 2 of Table 4, excluding glucose as a covariate.

The researchers chose not to exclude men with high alcohol intake. I would recommend excluding these subjects from the main analyses. Alternatively, the authors should explain the reason for including these subjects and perform the analyses included in table 4, also excluding men with high alcohol intake.

RESPONSE
We included all subjects in our main analyses because fatty liver has multiple causes, and the relative contribution of high ethanol intake in the aetiology of FLD is undetermined. We have explained this in our discussion. See page 21, lines 14-19.

Please, check the use of the term "subjects" throughout the manuscript. This term should be substituted by the term "men", especially in the conclusions. This is more informative to the reader. - The discussion is too long.
RESPONSE:
The term “subjects” has been replaced with “men” where deemed appropriate, especially in the conclusions.

To Reviewer 2
I suggest authors run an additional sensitivity analysis excluding smokers given that smoking can be have a large confounding effect in observational studies? This will strengthen the robustness of their findings.
Can you also please revise your baseline results, which state that there are less smokers in the high FLI group, as this was not statistically significant.

Abstract line 17: Please add "for T2D" following increased risk.

RESPONSE:
We thank the reviewer for the suggestions. We ran additional sensitivity analysis excluding smokers. The finding of similar result has been mentioned in the result (under sensitivity analyses) and discussion. The table showing the results (Table 5) are available as supplementary file (appendix). The baseline data show that the mean quantity of smoked by the men in high FLI category was lower than the mean in the low and middle FLI categories, and this was not statistically significant. The statement referring to this in the result section has been revised by deletion of comparison phrase “but a lower proportion of smokers”.
"for T2D" has been added following increased risk in line 17 of the abstract.

To reviewer 3
As far as the outcome T2DM, was self-report sufficient or did there need to be confirmation in registries? How often was T2DM ascertained by the various methods?

Neither FLI nor MS are "diseases" or even "conditions"... rather constellations of risk factors. Pending confirmation of statistical methods, and ? understanding the differences between this analysis and that of Karajamaki, would the authors comment from a health systems perspective on which parameters / risk factors would be most cost-effective to screen for in asymptomatic patients (men), and when further studies might be required? OGTT re T2DM? Ultrasound / other radiology / biopsy? re NAFLD/NASH?

RESPONSE:
We appreciate the reviewer’s comments or concerns. Self-reported physician confirmed diagnosis of type 2 diabetes was enough. However, detection of T2D by self-report of physician diagnosed T2D was followed by either detection via the hospital discharge registers or National drug reimbursement register. Therefore, these have been excluded from the analyses. Incident T2D was by record linkage with registers. We have revised the statement on outcome definition to reflect this. The proportion of the data obtained by the record linkage are as follows:
Hospital discharge registers 42%
National drug reimbursement register: 58%
This has also been stated in the text. Please see outcome definition.

We have commented on the more cost effective parameter from a health system’s perspective has been added. See Page 23 lines 20-23.

VERSION 2 – REVIEW

REVIEWER	Dimitrios Koutoukidis University of Oxford
REVIEW RETURNED	13-Apr-2019

GENERAL COMMENTS	I am happy with the authors response. Please correct typo in p4, line 20. Please correct typo in p11, line 13 (needs to be 6.2). Delete "it is remarkable that" from p21, line20. Delete "especially" from the conclusion p25 line 3, as the study was only in men.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

RESPONSE:

We thank the reviewers for their detailed review and the recommendation of publication of our manuscript.

Reviewer 2

Please correct typo in p4, line 20.

Please correct typo in p11, line 13 (needs to be 6.2).

Delete "it is remarkable that" from p21, line20.

Delete "especially" from the conclusion p25 line 3, as the study was only in men.

RESPONSE:

The typo in p4, line 20 has been corrected.

The typo in p11, line 13 has been corrected.

"it is remarkable that" on p21, has been deleted.

"especially" in the conclusion on p25 line 3, has been deleted.